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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/551,977
Filing Date: April 14, 2000
Appellant(s): POLO ET AL.

ROBINS &PASTERNAK LLP
For Appellant

EXAMINER'S ANSWER

This is in response to the reply brief filed on December 07, 2005 and the Order Returning Undocked Appeal to Examiner of February 07, 2006, the examiner's Answer of October 05, 2005 is hereby vacated to permit entry of the following Examiner's Answer in accordance with the new rules effective September 13, 2004.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

Appellants' statement related to the interference is correct.

The examiner is not aware of any related appeals, interferences, or judicial proceedings, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

NABI protein database: AAC 83379, AAO 33347, AAO33325, AAA 96973.

(9) Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17 and 19, 21-23 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application filed, had possession of the claimed invention. In the instant case, the specification only teach that they have isolated a mutated Sindbis virus vector that is able to infect human dendritic cells (DC), which comprises a substantive mutation at amino acid residue 160 of Gly for Glu of said Sindbis virus (SIN) E2 protein. However, Applicants do not have a possession for having any other alphavirus vector made by a mutated alphavirus with a mutation corresponding to the amino acid residue 158-162 of E2 protein of SIN, which is able to infect human DC (Office Action mailed on June 03, 2004).

Whether the appellants have the possession of claimed invention is related to the factors set forth below: 1). Level of skill in the art; 2). Method of making it; 3). Complete or partial structure; 4). Physical and/or biological properties; and 5). Correlation between structure.

In the instant case, Alphaviruses are a group of arthropod-bone viruses in Togaviridae family wildly distributed in the animal kingdom and human being and persisted in nature through a particular life circle from a mosquito to vertebrate. The family of the viruses comprises twenty-six known virus and virus serotype as well as many isolates. While all alphaviruses are genetically, structurally and serologically related as they all comprise two to three structural envelope proteins (E1- E3) and four non-structural proteins (NPS1-4), the genomes of alphaviruses consisting of a single molecule of linear, positive-sense, single-stranded RNA vary in size from 9.7-11.8 kb. For examples, most alphaviruses comprise E1 and E2 envelope proteins

with molecular weights from 45,000-58,000. Some alphaviruses have a third envelope protein E3. Moreover, alphaviruse is a RNA virus; it mutates from one isolate to another. The genetic codes and sizes of the E2 glycoproteins change with different alphaviruses or even among the different isolates too. Therefore, even the procedure of making E2 glycoprotein mutation and assay of testing human dendritic cell infectivity are all well known in the art, they make no reference for a mutated alphavirus still in question. In fact, up-to-date, only one paper has been published by the appellants' group post filling date (J. Virol. (December 2000, Vol. 74, pp. 11849-11857), which reports that only one single substitutive mutation of Gly for Glu at 160 of SIN E2 changes the SIN to become human DC tropic virus.

The broad scope of the claimed invention reads on any other alphavirus vector made by mutated alphaviruses with a mutation corresponding to the amino acid residues 158-162 of SIN E2, which is able to infect human DC. As described above, alphaviruses have many members and isolates, which vary in sizes and genetic codes, the precise mutations in term of amino acid substitution and position for each alphavirus are probably not the same compared to the SIN E2. For example, the amino acid sequences of SIN E2 proteins vary among the different isolates (Accessory number AAA96973, AAO33325, AAO33347 and AAC83379), which is also very much different from the E2 protein of other alphavirus, such as Semliki Forest virus (Accessory number NP 819006). The specification does not teach which position is correspond to the amino acid residues from 158 to 162, and which position from 158 to 162 is important for the substitutive mutation, and which kind of amino acid should be used for the substitution for any or all claimed alphavirus. The specification lacks of teaching any more complete or partial sequence of mutated E2 for all claimed alphaviruses or the physical and/or biological properties of the other mutants except the claimed Sindbit virus. The specification is deficient for describing any correlation between the structure and function for each amino acid residues in the locations from 158 to 162 corresponding to the claimed Sindbis virus except the position 160 with Gly for Glun substitutive mutation. For example, Semliki Forest virus (NP 819006) does not have Glu at position 160 in addition to many other genetic codes different in E2. Therefore, it probably exhibit different biological function caused by its 1st to 4th dimensional or tertiary structure of the protein. While the technique and sequence are available for making the mutation, they still make no reference for the particular mutated alphavirus in question.

MPEP cites: "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S. Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991)." In the instant case, there is no any reduction to practice all species of the claimed mutated alphavirus genus that has been referred in application (page 21, lines 5-19); therefore, it concludes that the appellants do not have the possession of all other claimed mutated alphavirus vectors.

Appellants assert in the Appeal Brief that the specification has more than enough of description of all claimed alphavirus mutants and one single species of SIN mutant with mutation of Gly for Glu at position 160 of E2 can be used for represent the claimed genus of all alphavirus mutants having mutant at position(s) corresponding to the amino acid residues from 158 to162 of SIN E2.

(10). Response to Argument.

Appellants' reply brief filed on December 25, 2005 has been acknowledged. The current office action is to response to the argument present in the reply brief.

In the reply, Appellants have addressed several points set forth below for overcoming the 112 1st paragraph written description rejection:

1). Appellants assert that it is irrelevant to claims relating to E2 some alphvirus contains a third (E3) protein cited in the examiner's answer.

2). Specification as filed satisfies the requirements of ***35 USC § 11, first paragraph.*** Specification contains a literal description of the claimed subject matter; the Examiner errs in contending that all species of the claimed mutated alphavirus genus" must to be reduced to practice in order to evince possession (pages 5-9 of the examiner's answer). Appellants further assert that when the E2 sequences of these (and other alphaviruses) were well known and could be readily aligned with the prototype SIN to determine residues corresponding to 158-162, is

inappropriate to inquire the specification describe particular mutations for each and every alphavirus species. (see last paragraph of reply brief).

3). The examiner fails to response to Dr. Polo's Declaration that has addressed the written description issue.

Appellants' argument has been respectfully considered; however, it is not found persuasive for overcoming the rejection for the following reasons:

1). At the offset, though examiner cites in the examiner's answer that some alphvirus contains a third (E3) protein, examiner did not use E3 to indicate that the variants of E2 are caused by presence of E3. More importantly, the examiner in the previous examiner's answer cites that most alphaviruses comprise E1 and E2 envelope proteins with molecular weights from 45,000-58,000. The genetic codes and sizes of the E2 glycoproteins change with different alphaviruses or even among the different isolates too. Therefore, even the procedure of making E2 glycoprotein mutation and assay of testing human dendritic cell infectivity are all well known in the art, they make no reference for a mutated alphavirus still in question. The examiner further cites several alphaviruses isolates such as AAA96973, AAO33325, AAO33347 and AAC83379 (NCBI protein data base cited in the previous examiner's answer, see attachment). If you take a close look at the structures of these isolates, you will find that each of them has different amino acid sequence. For example, the alphavirus with Accessory number **AAA96973** has 424 amino acids for its E2 protein, the amino acid residues of said E2 protein from 158 to 162 are **KIPLT.** The alphvirus with Accessory number **AAO33325** has 423 amino acid residues for its E2 protein; the amino acids from 158-162 are **KETTA**. The alphavirus with Accessory number **AAO33347** has 521 amino acid residues in its E2 protein; the amino acids from 158 to 160 of said E2 protein are **TREEI**. The alphavirus with Accessory number **AAC83379** has 423 amino acids for its E2 protein; the amino acids from 158 to 162 of said E2 protein are **NIPCR**. Nevertheless, the sequences of these five amino acids **KIPLT, KETTA, TREEI** and **NIPCR** vary greatly and shear very low homology. The examiner also cited in the previous examiner's answer that the genomes of alphaviruses are different in lengths (e.g. Sindbis virus (SIN) has 11703 bp, Venezuelan equine encephalitis virus (EEV) has 11444 bp, Semliki forest virus (SF) has 11442 bp, Ross River virus (RR) has 11657 bp). Therefore, sequences of E2 envelope protein vary greatly. The alignment of N-terminal starting regions of the E2 glycoproteins among

the all members of alphavirus relative to SIN would not be same too, and the relative positions corresponding to amino acid residues of 158-162 of SIN E2 among different alphaviruses are undefined by the specification and universally accepted or recognized by the state of art. Even if the relative position may be measurable by taking length of times for a person skill in the art, which is only an enablement issue and is separate problem from the written description since the mutations for all other species of the claimed alphaviruses have not bee defined yet. In view large members of the alphaviruses in the art, and their different genetic structures, especially in that claimed region, only one single species of SIN E2 mutation of Gly for Glu at amino acid residue 160 cannot represent all alphaviruses mutant as claimed drafted (page 10 of previous examiner's answer).

Appellants argue this particular region that the scope of the claimed invention only encompass five amino acid residues from 158 to 162, it is not so broad. However, this statement is not so accurate. In fact, the broad scope of the claims read on any or all alphavirus. According to the specification, there are at least 41 have been intended (See page 21, lines 5-19), if we only calculate the substitution mutation at amino acid residues 158-162, there are 19 (20-1) amino acids that can be used for the substitution, the variants for the 5 positions with 19 possible alternations of amino acids for all alphaviruses encompassed in claim 17 is huge (Σ= 19 x (5+4+3+2+1) x all alphavirues existed). Therefore, the scope of the claim 17 is very abroad, and it include innumerous species of alphaviruses.

Appellant assert that the specification has literal description of claimed invention, the specification has been carefully reviewed, however, the examiner cannot find that the specification gives any adequate description regarding the structural and functional characteristics and/or relationship of this five amino acid residues in common among different alphaviruses. The claimed Sindbis virus capable of infecting human dendrite cell is an unexpected result that is coming from a random selection without involvement any consensus sequence involvement of E2 glycoprotein of all alphavirus. For example, appellants do not describe in the specification regarding what kind of amino acid residue(s) is conserved in this region and what kind of amino acid residue(s) in this region contribute the human dendrite cell tropism and what kind of amino acid should be substituted or presented in order to confer the human dendrite cell susceptibility. Because the specification lacks of explanation about why the

Gly for Glu mutation in the position 160 of E2 makes the Sandbags virus becomes human dendrite cell tropic, and this type of mutant is not a conventional in the art, a person skill in the art would not recognize that the appellant s should have the possession of genus of any or all mutant alphaviruses.

Appellants allege that examiner errs in attending to requiring that all species of the claimed mutated alphavirus genus" must to be reduced to practice in order to evince possession (pages 5-9 of the examiner's answer). This is not correct because in pages 5-6 of examiner's answer, the examiner does not inquire appellants to describe each and every species of the genus alphavirus, the examiner's answer clearly cites that "According to MPEP: To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably concluded that the inventor had possession of the claimed invention. The possession of claimed invention can be shown by describing the claimed invention with all of its limitation in the specification including a drawing or description of an actual reduction to practice. The written description may arise in the following situations: a). The claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention; b). The claimed invention as a whole may not adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art; and c). The invention is described solely in terms of a method of its making coupled with its function and there is no described or art recognized correlation or relationship between the structure of the invention and its function etc."

In the previous examiner's answer, the examiner is focused on whether a single disclosure can represent huge numbers of species that the broad scope of claim covered as described above and in the previous examiner's answer. Some of them are set forth bellow (pages 8-10):

The specification lacks sufficiently description that one skilled in the art would recognize that the appellants had possession of the claimed invention. Alphaviruses are a group of arthropod-bone viruses in Togaviridae family wildly distributed in the animal kingdom and human being, and persisted in nature through a particular life circle from a mosquito to vertebrate. The family of the viruses comprises twenty-six known virus and virus serotype as

well as many isolates. While all alphaviruses are genetically, structurally and serologically related as they all comprises two to three structural envelope proteins E1- E3 and fore non-structural proteins, the genomes consisting of a single molecule of linear, positive-sense, single-stranded RNA vary in size from 9.7-11.8 kb. While the appellants have cited many species or isolates of alphaviruses in the specification (pages 21, lines 5-19), The specification on pages 1-5, 21 and 32 only cites many alphaviruses existed in the art. The description of other alphavirus that may be mutated in E2 and become human dendritice cell tropism is only hypothetically mentioned. In fact, the specification does not adequately description about how other alphavirus is mutated in E2 since they may have different genetic codes, especially in that claimed region. There is not any example teaching how other alphavirus is mutated in E2 and what the activity of such E2 mutant. The family of alphavirus as applicants stated contains many viruses (at least 38 different viruses that applicants cited in the specification for the claimed alphaviruses referred to), it is well known in the art that each of them is different in length and genetic codes, the alignment of each alphavirus with SIN would be different and amino acid residues are not same as SIN E2. The specification does not teach how the homologous and consensus sequence for so many alphaviruses are analyzed compared to the SIN. A person skill in the art would not recognize the appellants having the possession of genus of the mutant alphavirus.

Moreover, the claimed invention as a whole is not adequately described in the specification, the claims invention requires an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. For example, the specification does not teach which position correspond to the amino acid residue 158-160 of Sindbis virus E2 is important for the amino a acid substitutive mutation, and which kind of amino acid should be used for the substitution, such as more acidic or more basic or more neutral amino acid should be used for the substitution. Because this type of mutant is not conventional in the art, a person skill in the art would also not recognize the appellants having the possession of genus of the mutant alphavirus if appellants lack of description the mechanism why the Gly for Glu mutation in position E160 make the virus having such dramatic change.

MPEP also cites: "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such

as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991)." Apparently, as described above, there is no reduction of practice of claimed invention disclosed in the specification.

Regarding to case law of Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991), MPEP cites: "The written description requirement is separate and distinct from the enablement requirement. In re Barker, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) (While acknowledging that some of its cases concerning the written description requirement and the enablement requirement are confusing, the Federal Circuit reaffirmed that under 35 U.S.C. 112, first paragraph, the written description requirement is separate and distinct from the enablement requirement and gave an example thereof.)" In the current case, while some sequences of alphaviruses and method of testing a virus infection for human dendritic cells are available in the art, the enablement issue is separate from the written description problem, they do not make any reference for the claimed product still in question."

The examiner's answer further contest that Appellants assert that disclosure of a single species can satisfy the written description requirement, which cites:

"MPEP cites: The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i) (C), above). See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. A "representative number of species" means that the species, which are adequately described, are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The**

disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004) ("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed.

In the instant case, the genus of the alpphavirus contains many members of viruses as appellants cited in the specification. Some of the alphavirus sequences are available in the art, and the technique of testing the mutated alphavirus as a human dendritic cells tropism has been taught in the specification. However, the genomes of alphaviruses are different in lengths (e.g. Sindbit virus (SIN) has 11703 bp, Venezuelan equine encephalitis virus (EEV) has 11444 bp, Semliki forest virus (SF) has 11442 bp, Ross River virus (RR) has 11657 bp). Therefore, sequences of E2 envelope protein vary greatly. The alignment of N-terminal starting regions of the E2 glycoproteins among the all members of alphavirus relative to SIN would not be same too, and the relative positions corresponding to amino acid residues of 158-162 of SIN E2 among different alphaviruses are undefined by the specification and universally accepted or recognized by the state of art. Even if the relative position may be measurable by taking length of times for a person skill in the art, which is only an enablement issue and is separate problem from the written description since the mutations for all other species of the claimed alphaviruses have not bee defined yet. In view large members of the alphaviruses in the art, and their different genetic structures, especially in that claimed region, only one single species of SIN E2 mutation of Gly for Glu at amino acid residue 160 cannot represent all alphaviruses mutant as claimed drafted.

As discussed above, the examiner does not agree that the Appellants are deemed to have invented all species of the large family of alphavirus genus if only one single mutant occurred in

one strain of Sindbit virus is taught in the specification, and there are so many other alphavirus is still in question.

Regarding to the Dr. Polo's Declaration filed on 07/28/2003, the argument has been respectfully considered; the following response is the examiner's answer in response to appellants request considering Dr. Polo's Declaration on the record.

Dr. Polo stated in the Declaration that 1) at the time of filling, both nucleotide and amino acid sequence of E2 proteins of many alphavirues were known and published. Moreover, even there is any unknown sequence, the person skill in the art is able to get it using conventional methods; 2). In light of the teaching of the specification, it would have been a routine for a typical scientist to mutate one or more of a amino acid residue(s) corresponding to residues 158-162 of E2; 3). To produce the alphavirus particle; and 4). To test the ability of a mutant alphavirus infectivity for human dendritic cells.

Dr. Polo's Declaration has been respectfully considered; however, it isn't persuasive to overcome the enablement rejection. Because apparently, the argument brought by Dr. Polo only argue that the methods for making E2 mutation and the method for testing the infectivity of such mutant to human dendrite cells are available if an alphavirus sequence is known; but the written description issue is dispensable from the enablement issue. Because it does not make it patentable if the alphavirus and its mutant actually are still in question.

MPEP cites: "The written description requirement is separate and distinct from the enablement requirement. In re Barker, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) (While acknowledging that some of its cases concerning the written description requirement and the enablement requirement are confusing, the Federal Circuit reaffirmed that under 35 U.S.C. 112, first paragraph, the written description requirement is separate and distinct from the enablement requirement and gave an example thereof.)".

As discussed above, there are many viruses in the genus of alphavirus family, Appellants will not be deemed to have invented species sufficient to constitute the large family of genus virus by virtue of only disclosing a single species of SIN mutant at only one single amino acid residue 160. In view of many alphaviruses with different lengths for their genetic codes in the art, the exactly position(s) corresponding to the amino acid residues 158-162 of the claimed SIN

E2 varies greatly and there is not reduction of practicing the claimed other species of alphavirus mutant by appellants. Therefore, the known sequences and available technique still make no reference to a non-isolated alphavirus mutant in question. Therefore, the Declaration can only overcome the enablement rejection, but it is not insufficient to overcome the written description rejection.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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